## SUPPORT FOR THE AMENDMENTS

Applicants have added new Claims 28-30. Support for new Claim 28 can be found on page 11, line 12 to 15, of the specification. Support for new Claim 29 can be found on page 11, lines 15 to 25, of the specification. Support for new Claim 30 can be found on page 11, line 12 to 25, of the specification.

No new matter has been added. Claims 1-30 are active in this application.

## REMARKS/ARGUMENTS

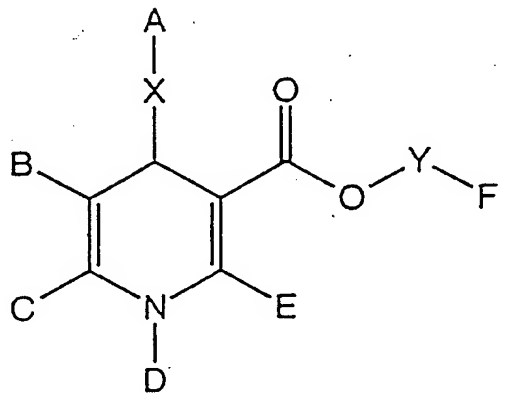
At the outset, Applicants wish to thank Examiner Morris for extending the search beyond the single disclosed compound which was elected for examination purposes.

Applicants also acknowledge the Examiner's statement that the claims have not been amended to the "elected compounds as asserted." However, Applicants never asserted that the claims had been limited to the elected ***compounds***. Instead, Applicants limited the claims the elected ***invention***. In the Restriction Response filed on March 25, 2004, Applicants elected Group I, Claims 2-11, 18, and 1, 12-17, and 19-21 (all in part) wherein F is formula (4), drawn to 1,4-DHPs. Applicants also elected a single disclosed species for examination purposes. In the Amendment filed on December 10, 2003, Applicants did indeed limit the claims to those compounds in which F is formula (4). Applicants did not limit the claims to the single disclosed compound elected for examination purposes and did not so state. Applicants submit that the appropriateness of the amendment is confirmed by the withdrawal of the objection to the claims as being drawn to an improper Markush group.

The rejection of Claims 1-25 under 35 U.S.C. §102(a) and/or 102(e) in view of U.S. Patent 6,350,766 (Uneyama et al US) and WO98/49144 (Uneyama et al WO); the rejection of Claims 1-27 under 35 U.S.C. §103(a) Uneyama et al US and Uneyama et al WO; and the

rejection of Claims 1-27 under the judicially-created doctrine of obviousness-type double patenting are respectfully traversed. At the outset, Applicants note that Uneyama et al WO is referred to as Niwa et al in the Office Action. However, Applicants will use the more conventional nomenclature and refer to this reference by the first-named inventor, rather than by the second-named inventor. In addition, Applicants note that Uneyama et al US corresponds to Uneyama et al WO as indicated on the front page of Uneyama et al US. Accordingly, Applicants will refer to the disclosure of Uneyama et al US in the following remarks.

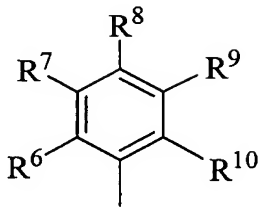
Uneyama et al US discloses certain dihydrpyridine compounds of the following general formula:




(1)

However, in Uneyama et al US, the group F is required to be:

> a group of following general formula (3), thiophene-3-yl group, thiophene-2-yl group, furan-3-yl group, furan-2-yl group, pyridine-4-yl group, pyridine-3-yl group, or pyridine-2-yl group:



(2)

wherein

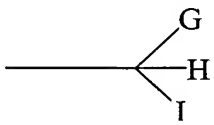
> $R^6$, $R^7$, $R^8$, $R^9$ and $R^{10}$ may be the same or different from each other, and each represent hydrogen atom, a halogen atom, hydroxyl group, carboxyl group, amino group, cyano group, nitro group, a lower alkyl group, a lower alkoxyl group, a lower alkenyl group, a lower alkynyl group, a lower alkylamino group, a lower alkylthio group, a lower alkanoyl group, a hydroxy-lower alkyl group, a hydroxy-lower alkoxyl group, a hydroxy-lower alkenyl group, a halogeno-lower alkyl group, a halogeno-lower alkoxyl group, a halogeno-lower alkenyl group, an aryl-lower alkoxyl group, a lower alkoxycarbonyl group or an aroyl group.

*See*, col. 3, line 3, to col. 4, line 3.

Moreover, the group Y is defined in Uneyama et al US so that it does not contain any type of aromatic ring or heterocyclic ring bonded to a saturated carbon atom. See, col. 4, lines 6-55.

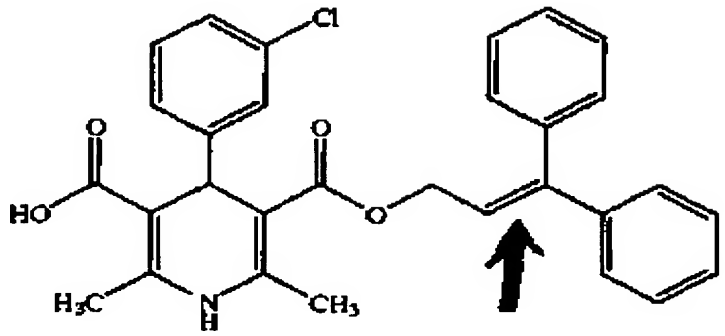
Thus, Uneyama et al US does not disclose any compounds in which F has the formula:

(4)



In fact, the compound cited in the Office Action and which appears at lines 53-54, of column 65, of Uneyama et al US (Example 53) has an unsaturated bond (*i.e.*, double bond) as shown below:

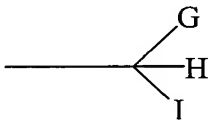
53




Thus, Uneyama et al US does not disclose any compounds in which either the group F, by itself, or the combination of the groups Y and F contain two aromatic or heterocyclic groups bonded to a saturated carbon atom.

In contrast, in the present claims, the group F is required to have formula (4):

(4)




wherein G and H may be the same or different from each other and each represent phenyl group, benzyl group, 1-naphthyl group, 2-naphthyl group, thiophene-3-yl group, thiophene-2-yl group, furan-3-yl group, furan-2-yl group, pyridine-4-yl group, pyridine-3-yl group, pyridine-2-yl group, pyridine-4-ylmethyl group, pyridine-3-ylmethyl group or pyridine-2-ylmethyl group, I represents hydrogen atom or hydroxyl group.

For this reason alone, neither Uneyama et al US nor Uneyama et al WO can anticipate the present claims.

As for the obviousness rejection, Applicants first note that Uneyama et al WO is already disclosed in the present specification (*see*, page 2, last line, to page 3, line 1). However, as explained in the specification, the compounds of Uneyama et al WO affect N-type calcium channels, but the selectivity thereof is not sufficiently strong so that the compounds are not actually used.

Under such circumstances, the present inventors have vigorously studied and as a result, they have found that the presently claimed compounds wherein one of features resides in the specific substituents F exhibit excellent selectivity. In other words, the activity of the presently claimed compounds against N-type calcium channels is similar to that of the compounds of Uneyama et al US and Uneyama et al WO, but the activity of the presently claimed compounds against L type calcium channels is very weak, so that the selectivity becomes very high. Thus, the presently claimed compounds are more selective than the compounds of Uneyama et al US and Uneyama et al WO. In support of this assertion, the Examiner's attention is directed to the following Tables A and B.

Table A corresponds to Table 10 appearing on page 127 of the present specification. On the other hand, Table B corresponds to Table 2 given in col. 69 of Uneyama et al US. In this connection, since the units of the data appearing in Table 2 are different from that of Table A, the units of the data appearing in Table 2 have been changed to agree with those in Table A. Specifically, the units for N-type inhibition and L-type inhibition in Table 2 were changed from 0.1 $\mu$M and IC50 nM to pIC50 and IC50$\mu$M, respectively, by calculation.

Table A

| Example | N-type inhibition (pIC50) | L-type inhibition (IC50 ($\mu$M)) |
|---|---|---|
| 12 | 5.4 | 2.69 |
| 14 | 5.7 | 4.27 |
| 20 | 5.5 | 2.88 |
| 23 | 5.8 | 1.82 |
| 33 | 5.8 | 1.70 |
| 54 | 5.7 | 1.58 |
| 57 | 5.8 | 1.78 |
| 60 | 5.8 | 3.89 |

Table B

| Example | N-type inhibition (pIC50) | L-type inhibition (IC50 ($\mu$M)) |
|---|---|---|
| 3 | 5.7 | 0.0063 |
| 8 | 6.1 | 0.032 |
| 9 | 5.4 | 0.082 |
| 14 | 4.6 | 0.050 |
| 20 | 5.7 | 0.250 |

By comparison of the data shown in Table A with the data shown in Table B, it is apparent that the both data on N-type inhibition are similar, which means that the N-type inhibition activities of the presently claimed compounds and those of Uneyama et al US and Uneyama et al WO are similar. In contrast, the IC50 data for L-type inhibition activities

(0.250 to 0.0063) of the compounds of Uneyama et al US and Uneyama et al WO are much smaller than those (1.58 to 4.27) for the presently claimed compounds, which means that the L-type inhibition activity of the compounds of Uneyama et al US and Uneyama et al WO is stronger than that of the presently claimed compounds. In other words, the selectivity of the presently claimed compounds is much higher than that of the compounds of Uneyama et al US and Uneyama et al WO.

Applicants submit that there is no teaching in any of the cited references which would suggest the improved selectivity of the presently claimed compounds. Accordingly, these results could not have been expected based on the teachings of the cited references and ensure the patentability of the present claims.

For these reasons, the rejection should be withdrawn.

The rejection of Claims 16-19 under 35 U.S.C. §101 is respectfully traversed. At the top of page 3 of the Office Action, it is asserted that Claims 16-19 are "drafted in terms of use." However, this assertion is incorrect. Claim 16 is directed toward N-type calcium channel antagonists, while Claims 17-19 are directed toward various therapeutic agents. Thus, none of Claims 16-19 are improper use claims, and the rejection should be withdrawn.

The rejection of Claims 16-19 and 21-23 under 35 U.S.C. §112, first paragraph, is respectfully traversed. Applicants submit that one of skill in the art would readily recognize the utility of the presently claimed compounds from the data provided in the specification. Moreover, one of skill in the art would clearly understand: (1) how to make and use the N-type calcium channel antagonists and therapeutic agents of Claims 16-19; and (2) how to carry out the methods of Claims 21-23. In support of these assertions, Applicants again point out the selective activity of the presently claimed compounds against N-type calcium channels and also the disclosure of the very reference cited by the Examiner:

It is said that the activation of N-type calcium channel is concerned with diseases such as encephalopathies caused by the ischemia in the acute phase after the onset of cerebral infarction, cerebral hemorrhage (including subarachnoidal bleeding) or the like; progressive neurodegenerative diseases, e.g. Alzheimer's disease; AIDS related dementia; Parkinson's disease; dementia caused by cerebrovascular disorders and ALS; neuropathy caused by head injury; various pains, e.g. sharp pain caused by spinal injury, diabetes or thromboangitis obliterans; pain after an operation; migraine and visceral pain; various diseases caused by psychogenic stress, e.g. bronchial asthma; unstable angina and hypersensitive colon inflammation; emotional disorder; and drug addiction withdrawal symptoms, e.g. ethanol addiction withdrawal symptoms. The compounds of the present invention are effective in inhibiting the activation of N-type calcium channel and, therefore, they are usable as remedies for the above-described diseases.

The calcium channels are now classified into subtypes L, N, P, Q, R and T. Each of the subtypes is distributed specifically to organs. Particularly, it is known that N-type calcium channel is widely distributed in the central nerves, peripheral nerves and adrenal medulla cells and that this calcium channel is concerned with the death of neurons, control of blood catecholamine dynamics and control of senses such as perceptivity.

It was confirmed that peptides, omega conotoxin GVIA and omega conotoxin MVIIA which selectively inhibit the function of N-type calcium channel inhibit the release of excitatory neurotransmitter from a brain slice sample. It was confirmed by animal experiments that they prevent the advancement of neuron necrosis in a cerebrovascular disorder. It is generally considered that a compound having a clinical effect of inhibiting the function of N-type calcium channel is effective in curing encephalopathies caused by the ischemia in the acute phase after the onset of cerebral infarction, cerebral hemorrhage (including subarachnoidal bleeding) or the like; progressive neurodegenerative diseases, e.g. Alzheimer's disease; AIDS related dementia; Parkinson's disease; dementia caused by cerebrovascular disorders and ALS; neuropathy caused by head injury. In addition, it was also confirmed by animal experiments that omega conotoxin MVIIA gets rid of formalin-caused sharp pain, hot plate pain, sharp pain caused by peripheral neuropathy, etc. Therefore, this medicine is considered to be clinically effective for relieving various pains such as sharp pain caused by spinal injury,diabetes or thromboangitis obliterans; pain after an operation; migraine; and visceral pain. Further, omega conotoxin GVIA inhibits the release of catecholamine from cultured sympathetic ganglion cells, the constriction reaction of an isolated blood vessel by the electric stimulation of governing nerves, and the acceleration of catecholamine secretion from dog adrenal medulla, etc. Therefore, it is considered that compounds having the N-type calcium channel-inhibiting activity are clinically effective in treating various diseases caused by psychogenic stress, e.g. bronchial asthma, unstable angina and hypersensitive colon inflammation [Neuropharmacol., 32, 1141 (1993)].

*See*, Uneyama et al US, at col. 1, line 9, to col. 2, line 2.

In addition, the Examiner's attention is directed to Claims 41 -60 of Uneyama et al US.

For these reasons, the rejection should be withdrawn.

The rejection of Claims 1, 5, 6. 10, and 12 under 35 U.S.C. §112, first paragraph, is respectfully traversed. As for the terms "heteroaryl group" and "heteroaryl lower alkyl group" applicants again submit that these terms are well known to those of skill in the art and are not indefinite and that one of skill in the art would have no trouble carrying out the present invention without undue experimentation. In particular, Applicants point to page 9, lines 1-4 and 13-15, where examples of such groups are disclosed.

For all of these reasons, the rejection should be withdrawn.

The rejection of Claims 1, 2, 16-19, 26, and 27 under 35 U.S.C. §112, second paragraph, is respectfully traversed. In particular, as noted above, Claims 16-19 are directed toward various N-type calcium channel antagonists and therapeutic agents which comprise a dihydropyridine or a salt thereof. In contrast, Claims 1 and 2 are directed to the dihydropyridines themselves or salts thereof. Accordingly, Claims 16-19 are not duplicates of Claims 1 and 2.

Thus, the rejection should be withdrawn.

Applicants submit that the application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

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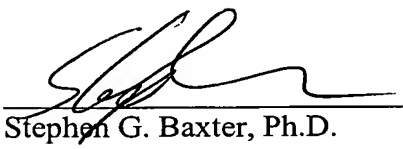

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